Drug Safety 2005; 28 (3): 183-189
0114-5916/05/0003-0183/$34.95/0

Do Selective Cyclo-Oxygenase-2 Inhibitors Have a Future?

Bernard Bannwarth

Department of Rheumatology, Pellegrin Hospital and Division of Therapeutics, Victor Segalen University, Bordeaux, France

Abstract

The dramatic withdrawal of rofecoxib on 30 September 2004, along with safety concerns about other cyclo-oxygenase (COX)-2 inhibitors (especially valdecoxib), raises important issues for clinicians, pharmaceutical companies and regulatory authorities. Some of these are examined in this article, including: (i) was the cardiotoxicity of rofecoxib evident long before its withdrawal?; (ii) is the thrombotic hazard a class effect that is applicable to all COX-2 inhibitors?; (iii) may conventional NSAIDs also confer a risk of cardiovascular thrombosis?; and (iv) is there any future for selective COX-2 inhibitors?

On 30 September 2004, Merck & Co. announced an immediate worldwide withdrawal of rofecoxib (Vioxx®)[1]. The decision was based on an interim analysis of a prospective, randomised, placebo-controlled, double-blind trial: the APPROVe (Adenomatous Polyp Prevention on Vioxx®) trial, which was designed to evaluate the efficacy of rofecoxib 25 mg/day in preventing the recurrence of large bowel polyps in 2600 patients with a history of colorectal adenomas. The 3-year data from this study indicated that after 18 months of treatment, patients receiving rofecoxib had almost twice the risk of cardiovascular events compared with those taking placebo.[1,2] The rate of confirmed myocardial infarction (MI) and stroke was 3.5% in the rofecoxib arm versus 1.9% in the placebo arm (absolute risk increase 1.6%; 95% CI 0.3, 2.8).[2]

The dramatic withdrawal of rofecoxib raises important issues for clinicians, pharmaceutical companies and regulatory authorities.[1-6] Some of these are examined in this editorial.

1. Was the Cardiotoxicity of Rofecoxib Evident Long Before its Removal?

Prior to the release of findings from the VIGOR (Vioxx® Gastrointestinal Outcomes Research) trial, several pharmacological studies led to concerns of a potential prothrombotic risk with cyclo-oxygenase (COX)-2 inhibition.[7]

Warnings that the pharmacologically-based concerns translated to clinical concern emerged with the report of the VIGOR trial at the end of November 2000. This study compared the occurrence of clinically important upper gastrointestinal events with rofecoxib 50 mg/day or naproxen 1000 mg/day in 8076 patients with rheumatoid arthritis who were treated for a median period of 9 months. Although the VIGOR trial provided robust evidence for the gastrointestinal safety of rofecoxib, it demonstrated relative risks of developing either a serious thrombotic cardiovascular adverse event or a MI with rofecoxib compared with naproxen of 2.38 (95% CI 1.39, 4.00) and 5.00 (95% CI 1.72, 14.29), respec-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

tively.[6,8] Given the small absolute number of cardiovascular events (<70), it could not be ruled out that this finding might have reflected the play of chance.[9] In that respect, a recent clinical trial that investigated the chemopreventive effects of low-dose aspirin (acetylsalicylic acid) on colorectal adenomas found a paradoxically higher frequency of MI and stroke in patients given aspirin 81 mg/day (1.06%, 4 of 377 patients) or 325 mg/day (2.69%, 10 of 372 patients) than those receiving placebo (0.27%, 1 of 372 patients), which was a difference that was regarded as being compatible with chance.[10]

Alternatively, the results of VIGOR could be explained by a prothrombotic effect of rofecoxib and/or a cardioprotective effect of naproxen.[9] The former hypothesis was supported by the pharmacological evidence, whereas the latter appeared to be supported by retrospective analyses of randomised controlled data of rofecoxib. These concluded that the risk of a cardiovascular thrombotic event was similar between rofecoxib and placebo or non-naproxen NSAIDs, but was significantly higher relative to naproxen.[7] However, *post hoc* analyses may have underestimated the magnitude of the cardiovascular hazard of rofecoxib for two main reasons: (i) the low cardiovascular risk of the population studied; and (ii) cardiovascular events were not pre-specified endpoints in the earliest trials.[7,11] Subsequently, retrospective pharmacoepidemiological observational studies failed to provide consistent findings.[7,12,13] All in all, these studies suggested that rofecoxib was associated with an elevated risk of thrombotic events compared with celecoxib and that rofecoxib use at dosages of >25 mg/day led to a significant increase in such events compared with no NSAID use.[7,12,13] Conversely, the studies did not reveal an excess risk among users of rofecoxib at dosages of ≤25 mg/day, which was the recommended dose regimen for long-term use.[7,12,13] Moreover, epidemiological studies were divided regarding the cardioprotective effect of naproxen.[7,14] In view of their inherent biases, epidemiological studies raised more questions than they answered.[5,7] Ideally, to settle the issues raised by VIGOR, a long-term outcome trial that focused specifically on cardiovascular events should have been carried out in patients reflecting 'real life' and receiving either placebo or the usual therapeutic doses of both rofecoxib and naproxen. Whether such a study would have been considered ethically acceptable in patients with rheumatic diseases is questionable.

In summary, there were strong signals of a cardiovascular hazard of rofecoxib as early as late 2000. There has been considerable controversy about whether these signals should have led to a more drastic decision than the mere changes in labelling ('black box warning') imposed by regulatory authorities, including the US FDA and the European Medicines Agency (EMEA). It may be argued that before the results of APPROVe were released, the scientific evidence of gastrointestinal benefit from rofecoxib appeared to outweigh the evidence of cardiovascular risk.[5,14]

A cumulative meta-analysis published a few weeks after the withdrawal of rofecoxib rekindled the controversy.[15] This meta-analysis included all randomised controlled trials in adult patients with chronic musculoskeletal disorders that compared rofecoxib 12.5–50 mg/day with other NSAIDs or placebo and used relevant files from the FDA. The analysis of the primary endpoint – MI – was based on 64 events, with 52 in patients receiving rofecoxib and 12 in control patients. By the end of 2000 (52 MIs, 20 742 patients), the relative risk (RR) was 2.30 (95% CI 1.22, 4.33) and 1 year later (64 MIs, 21 432 patients) it was 2.24 (95% CI 1.24, 4.02).[15] There was little evidence that the RR differed depending on the control group (placebo, non-naproxen NSAIDs or naproxen) or trial duration.[15] The authors concluded that "an increased risk of MI was evident from 2000 onwards", while acknowledging certain limitations in their analysis. For instance, data from the Alzheimer's Disease and Mild Cognitive Impairment programme were not included. Two placebo-controlled studies, together with interim data from an ongoing placebo-controlled study comprising 2899 elderly subjects, showed similar rates of cardiovascular events in the rofecoxib 25 mg/day and placebo groups.[7] In addition, 24 of 52 MIs

recorded by the end of 2000 came from the VIGOR trial, in which patients received rofecoxib 50 mg/day.[10] Finally, rofecoxib illustrates the difficulty of assessing the overall safety profile of a drug that has established (gastrointestinal) advantages together with possible (cardiovascular) disadvantages.

2. Is the Thrombotic Risk a Class Effect?

In the early 1990s, it was thought that inhibition of COX-2 accounted for the analgesic and anti-inflammatory properties, whereas inhibition of COX-1 accounted for the major adverse effects, of NSAIDs. The original flaw of selective COX-2 inhibitors was that they were developed on the basis of this appealing paradigm before it had been rigorously tested.[16] Coincident with the approval of the first two coxibs, celecoxib and rofecoxib in 1999, COX-2 was reported to be a major source of the endothelial cell-derived prostacyclin (PGI_2).[5,9,16] Since mature human platelets uniquely express COX-1, the source of thromboxane A_2 (TXA_2), coxibs, unlike conventional NSAIDs, could be expected to affect the balance between antithrombotic (PGI_2) and prothrombotic (TXA_2) eicosanoids, thereby promoting cardiovascular adverse events.[8,16] However, it had been emphasised that other endothelium-derived substances, including nitric oxide, might then counteract the actions of TXA_2.[9] Furthermore, it had been suggested that selective COX-2 inhibitors might potentially have antiatherogenic effects by virtue of inhibiting inflammation in atheromatous plaques.[8] Nonetheless, the pharmacological evidence supported the hypothesis that it was biologically plausible that COX-2 inhibition might lead to serious cardiovascular complications, especially in at-risk individuals.[7] If so, the cardiovascular hazard might be a class effect applicable to all selective COX-2 inhibitors.[3] A study of valdecoxib and its injectable prodrug parecoxib, revealed a clustering of cardiovascular events (along with a significantly greater incidence of sternal wound infection) in the treated versus placebo control groups in patients undergoing coronary artery bypass grafting (CABG) surgery.[17] According to a meta-analysis presented at the 2004 American Heart Association Scientific Sessions, valdecoxib was associated with twice as many MIs and stroke events as placebo (RR 2.19; 95% CI 1.19, 4.03) in placebo-controlled studies involving a total of 7500 patients, including 2000 patients who had undergone CABG surgery.[18] Conversely, the CLASS (Celecoxib Long-term Arthritis Safety Study) trial, which comprised 8059 patients with either osteoarthritis (72%) or rheumatoid arthritis (28%), demonstrated no significant difference in cardiovascular events between celecoxib 800 mg/day and the comparator NSAIDs, ibuprofen 2400 mg/day or diclofenac 150 mg/day.[19] Besides the differences in trial designs and control NSAID comparators between the VIGOR and CLASS trials, and along with methodological concerns, pharmacological differences between rofecoxib and celecoxib might have contributed to the discrepant findings of these studies.[7] Unlike rofecoxib, celecoxib loses its COX-2 selectivity at a supratherapeutic dose, such as that used in CLASS.[7] Of note, CLASS did not show that celecoxib had a better safety record for upper gastrointestinal ulcer complications than ibuprofen or diclofenac.[19]

Taken together, these data suggest that the cardiovascular thrombotic hazard might be specific to highly selective COX-2 inhibitors such as rofecoxib, valdecoxib, etoricoxib or lumiracoxib. However, TARGET (Therapeutic Arthritis Research and Gastrointestinal Event Trial), which enrolled 18 325 patients with osteoarthritis, failed to demonstrate any significant increase in thrombosis risk associated with lumiracoxib 400 mg/day (twice the maximal recommended dose for osteoarthritis) compared with ibuprofen 2400 mg/day or naproxen 1000 mg/day, although some authors have shown concern about a numerical excess of MIs in the lumiracoxib arm compared with the naproxen arm.[20]

In contrast to the view that an increased thrombotic risk is only associated with highly selective coxibs, concerns that celecoxib might present an increased risk of thrombotic events remained. The Uppsala Monitoring Centre signalled the possibility of serious cardiovascular events associated with COX-2 inhibitors as early as 2000–2001.[21] On 17

December 2004, the US National Cancer Institutes announced the premature cessation of the APC (Adenoma Prevention with Celecoxib) trial because of a significant excess of major cardiovascular events (deaths, MIs and stroke). This was a three-arm randomised trial of 2026 patients given celecoxib (400 mg/day or 800 mg/day) or placebo for an average of 33 months.[22] A significant excess of major cardiovascular events was observed, with a dose-response effect. The odds ratios were 2.5 (95% CI 1.0, 7.0) and 3.5 (95% CI 1.4, 9.3) for celecoxib 400 mg/day and 800 mg/day, respectively.[22] However, a similar trial (PreSAP [Prevention of Spontaneous Adenomatous Polyps]) that was conducted in parallel to the APC trial has not shown any increased hazard with celecoxib.[22]

However, a few days later, on 20 December 2004, the US National Institutes of Health announced the premature cessation of ADAPT (Alzheimer Disease Anti-inflammatory Prevention Trial).[22] While the study of approximately 2400 patients with an average of 3 years of follow-up was being reviewed for potential adverse effects with celecoxib, an excess of cardiovascular events was found in patients assigned to naproxen 440 mg/day versus placebo.[22] Conversely, celecoxib 400 mg/day did not appear to confer a risk of thrombotic events in this study. How could these apparently conflicting findings be explained?

It is well appreciated that all NSAIDs, including coxibs, may increase blood pressure and attenuate the effects of antihypertensive medications through inhibition of COX-1 and/or COX-2 dependent prostaglandins in the kidney and possibly additional mechanisms.[7,11,23] The increase in blood pressure depends on individual susceptibility as well as on the NSAID dose and probably also on the compound used. This increase, albeit usually modest (a few mm Hg on average), may have significant clinical consequences.[23] It has been reported that a 3mm Hg increase in systolic blood pressure over 1 year resulted in a 4% increase in the occurrence of ischaemic heart disease and stroke events in US adults with osteoarthritis or rheumatoid arthritis.[24] Thus, prolonged therapy with any NSAID may lead to ischaemic heart diseases and stroke, especially in patients with pre-existing hypertension or other cardiovascular risk factors.[23] In the placebo-controlled APPROVe trial, blood pressure was elevated in patients in the rofecoxib group early in the course of the study, but the incidence of MI and stroke in the two groups began to diverge after a year or more of treatment.[5] These features are compatible with the hypothesis that the cardiovascular thrombotic effects of rofecoxib in this study may primarily be ascribable to the drug effects on blood pressure. In the absence of full analyses of APC and ADAPT data, it would be hazardous to propose a similar mechanistic explanation for their findings. However, it is worthy of note that the cardiovascular hazards of celecoxib and naproxen have only been observed in studies conducted over several years. Interestingly, a press release issued by the EMEA on 22 December 2004 reported that "a preliminary assessment of the summary data, whilst not conclusive, indicates that an increased risk of serious cardiovascular events seen in the APC trial may be related to the dose and duration of treatment". Whether the discrepant findings of long-term celecoxib trials were related to varying levels of cardiovascular risk factors across the populations studied should also deserve careful examination.

In summary, both traditional NSAIDs and coxibs, in a dose-related way, are capable of inducing an increase in blood pressure. Accordingly, both have the potential of causing cardiovascular thrombotic effects, particularly in predisposed patients. It ensues that: (i) physicians should pay careful attention to the patients' cardiovascular profile before prescribing an NSAID inasmuch as salt and water retention induced by conventional and COX-2 selective NSAIDs can precipitate cardiac failure; (ii) NSAIDs, *when indicated*, must be prescribed at the minimal effective dose for the minimal requisite period of time; and (iii) long-term use, *if needed*, requires appropriate monitoring, including regular blood pressure monitoring.

A second mechanism may underlie the cardiovascular thrombotic hazard of selective COX-2 inhibitors. By inhibiting PGI_2 production while leav-

ing the TXA_2 generation unaffected, coxibs could exacerbate a tendency towards thrombosis, especially in clinical syndromes associated with platelet activation, such as unstable angina, peripheral arterial obstructive disease and cerebral ischaemia, or in situations where the risk of peripheral venous thrombosis is high, such as immobilisation as a result of surgery.[7] This mechanism could be the cause of acute thrombotic events that may, therefore, occur even during short-term treatment. Whether this particular mechanism is common to all coxibs is uncertain. The EMEA and FDA are currently conducting a review of all COX-2 inhibitors, looking at cardiovascular safety. Pending the outcome of these reviews, national regulatory authorities of various countries, including France and the UK, have advised practitioners against using any coxib in patients with established ischaemic heart disease or cerebrovascular disease.

3. Is There Any Future for Selective Cyclo-Oxygenase-2 Inhibitors?

The first problem with which we are faced concerns the already approved compounds. Regarding celecoxib, there is still little evidence that its cardiovascular and gastrointestinal risk profile differs markedly from that of conventional NSAIDs, which is a picture that is consistent with its COX-2 selectivity that is similar to that of some older drugs, such as diclofenac and meloxicam.[14] No safety concern has been raised about etoricoxib, but more information on its cardiovascular effects is awaited from the ongoing large-scale MEDAL (Multinational Etoricoxib versus Diclofenac Arthritis Long-term) trial. The fate of valdecoxib/parecoxib is much debated.[22,25] In addition to concerns about the cardiovascular safety of valdecoxib, there have been reports of serious hypersensitivity and skin reactions, some with fatal outcome, including erythema multiforme and toxic epidermal necrolysis. According to an EMEA public statement published on 15 December 2004, the reported rates of these reactions appear to be greater for valdecoxib than for other COX-2 inhibitors. Moreover, valdecoxib has not been definitively confirmed as offering protection against upper gastrointestinal complications, and its clinical efficacy, as with that of other coxibs, was not found to be superior to that of conventional NSAIDs.[22] Subsequently, Ray et al.[25] recently recommended "that clinicians stop prescribing valdecoxib except in extraordinary circumstances".

The second difficult issue concerns those drugs under consideration and those in the pipeline. Which studies should be required to afford adequate assurance of their safety? This raises the issue of the appropriate threshold for drug approval by regulatory agencies.[1] Lumiracoxib can be used as an example to illustrate this problem.[20,26] TARGET, albeit the largest coxib trial to date, does not enable assessment of the actual benefit/risk ratio of lumiracoxib. It showed that the ulcer complications with lumiracoxib decreased by 66%, compared with ibuprofen and naproxen. However, the absolute risk reduction (0.59%) was much less impressive and the benefit of lumiracoxib was no longer observed in patients taking low-dose aspirin for cardiovascular prophylaxis. Furthermore, combination with a proton pump inhibitor would have reduced the gastrotoxicity of the traditional NSAIDs used in this study. Concern has been raised about a possible hepatotoxic potential of lumiracoxib because there were more asymptomatic elevations in liver function tests, although not clinical hepatitis, in patients given lumiracoxib compared with those receiving comparator NSAIDs.[20,26] As already mentioned, concern has also been raised about a numerical excess of MIs with lumiracoxib compared with naproxen. Whatever the case, it should be stressed that the major drawback of TARGET was not that it was inadequately powered to detect significant differences in MI rates between the drugs studied, but that it excluded those patients with significant pre-existing coronary artery disease. Thus, patients enrolled in TARGET did not reflect the 'real world' osteoarthritic population. In fact, the cardiovascular hazard of valdecoxib/parecoxib has been revealed by a relatively small, short-term, randomised controlled trial that was conducted in patients at high risk of cardiovascular thrombotic events.[17] Whilst acknowledging the fact that premarketing trials are unable to

detect all of the adverse effects of a drug, especially the rare effects, randomised controlled trials should still be considered as the gold standard for testing a specific hypothesis, provided that the study participants are representative of the intended target treatment groups.[7]

Finally, it seems premature to envisage a collapse of the COX-2 inhibitor class. It is likely that these agents are not a uniform group of drugs. Coxibs, like conventional NSAIDs, might exhibit different adverse experience profiles as a result of differences in relative selectivity and potency as a COX-2 inhibitor, prostaglandin-independent pharmacological effects, chemical structures and pharmacokinetic characteristics.

4. Conclusion

Besides the key points examined in this editorial, the following lessons may be drawn following the dramatic withdrawal of rofecoxib:

1. The coxib story serves to remind clinicians that they must be aware of the fact that the adverse effect profile of a new drug is not, and indeed cannot be, completely known when the drug is introduced to the market. Accordingly, a new drug should be prescribed to selected patients only, at least in the earliest months or years of its release.
2. Since COX-2 inhibitors can no longer be viewed as a therapeutic breakthrough, there is the fear that the possibility of developing new compounds with improved safety compared with conventional NSAIDs will be precluded. Nitric oxide donating NSAIDs, as well as dual inhibitors of COX and 5-lipoxygenase, have been claimed to exert a broader range of anti-inflammatory actions while being less toxic than conventional NSAIDs.[27-29] However, these claims are poorly substantiated by clinical studies to date.[28,29]
3. There is an NSAID paradox. NSAID-associated gastropathy is a well-recognised major cause of iatrogenic pathology, which results in a significant increase in morbidity, hospitalisation and mortality, and causes a significant burden to the healthcare system. Although NSAIDs appear to differ in their gastrotoxicity, NSAID withdrawals have been caused by other safety reasons, such as hypersensitivity (alclofenac, zomepirac), flank pain syndrome (suprofen) or adverse reactions involving other organ systems, including the liver (benoxaprofen, bromfenac, ibufenac, pirprofen), the skin (benoxaprofen, fenclofenac, isoxicam), the bone marrow (oxyphenbutazone) and the cardiovascular system (rofecoxib).[30,31]

Acknowledgements

No sources of funding were used to assist in the preparation of this article. The author has attended Merck sponsored symposia as an invited speaker and was involved in clinical studies sponsored by Merck.

References

1. Vioxx: an unequal partnership between safety and efficacy. Lancet 2004; 364: 1287-8
2. Langton PE, Hankey GJ, Eikelboom JW. Cardiovascular safety of rofecoxib (Vioxx): lessons learned and unanswered questions. Med J Aust 2004; 181: 524-5
3. Dieppe PA, Ebrahim S, Martin RM, et al. Lessons from the withdrawal of rofecoxib. BMJ 2004; 329: 867-8
4. Topol EJ. Failing the public health: Rofecoxib, Merck, and the FDA. N Engl J Med 2004; 351: 1707-9
5. FitzGerald GA. Coxibs and cardiovascular disease. N Engl J Med 2004; 351: 1709-11
6. Horton R. Vioxx, the implosion of Merck, and aftershocks at the FDA. Lancet 2004; 364: 1995-6
7. Clark DWJ, Layton D, Shakir SAW. Do some inhibitors of COX-2 increase the risk of thromboembolic events? Linking pharmacology with pharmacoepidemiology. Drug Saf 2004; 27: 427-56
8. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 2001; 286: 954-9
9. FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. N Engl J Med 2001; 345: 433-42
10. Baron JA, Cole BF, Sandler RS, et al. A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med 2003; 348: 891-9
11. Mukherjee D. Selective cyclooxygenase-2 (COX-2) inhibitors and potential risk of cardiovascular events. Biochem Pharmacol 2002; 63: 817-21
12. Solomon DH, Schneeweiss S, Glynn RJ, et al. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. Circulation 2004; 109: 2068-73
13. Campen DH, Graham D, Cheetham C, et al. Risk of acute cardiac events among patients treated with cyclooxygenase-2 selective and non-selective-nonsteroidal antiinflammatory drugs [abstract 1756]. Arthritis Rheum 2004; 50 (9 Suppl.): S657
14. Meagher EA. Balancing gastroprotection and cardioprotection with selective cyclo-oxygenase-2 inhibitors: clinical implications. Drug Saf 2003; 26: 913-24

15. Jüni P, Nartey L, Reichenbach S, et al. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. Lancet 2004; 364: 2021-9
16. Lipsky PE, Brooks P, Crofford LJ, et al. Unresolved issues in the role of cyclooxygenase-2 in normal physiologic processes and disease. Arch Intern Med 2000; 160: 913-20
17. Ott E, Nussmeier NA, Duke PC, et al. Efficacy and safety of the cyclooxygenase-2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. J Thorac Cardiovasc Surg 2003; 125: 1481-92
18. FitzGerald G, Furberg C, Psaty B. Invited lecture at the American Heart Association Scientific Sessions 2004 [online]. Available from URL: http://www.jointandbone.org [Accessed 2005 Feb 3]
19. Jüni P, Rutjes AWS, Dieppe PA. Are selective COX-2 inhibitors superior to traditional non steroidal anti-inflammatory drugs? BMJ 2002; 324: 1287-8
20. Topol EJ, Falk GW. A coxib a day won't keep the doctor away. Lancet 2004; 364: 639-40
21. Cyclo-Oxygenase - 2 Inhibitors. WHO pharmaceuticals newsletter, 2004; 5: 7-8 [online]. Available from URL: http://www.who.int/medicines/library/pnewslet/5news2004.pdf [Accessed 2005 Feb 16]
22. Topol EJ. Arthritis medicines and cardiovascular events: 'house of coxibs'. JAMA 2005; 293: 366-8
23. Day R. Hypertension in the patients with arthritis: have we been underestimating its significance. J Rheumatol 2003; 30: 642-5
24. Singh G, Miller JD, Huse DM, et al. Consequences of increased systolic blood pressure in patients with osteoarthritis and rheumatoid arthritis. J Rheumatol 2003; 30: 714-9
25. Ray WA, Griffin MR, Stein CM. Cardiovascular toxicity of valdecoxib. N Engl J Med 2004; 351: 2767
26. Bannwarth B, Berenbaum F. Clinical pharmacology of lumiracoxib, a second generation COX-2 selective inhibitor. Exp Opin Invest Drugs. In press
27. Fiorucci S, Antonnelli E, Burgaud JL, et al. Nitric oxide-releasing NSAIDs. A review of their current status. Drug Saf 2001; 24: 801-11
28. Wallace JL, Del Soldato P. The therapeutic potential of NO-NSAIDs. Fundam Clin Pharmacol 2003; 17: 11-20
29. Bannwarth B. Is licofelone, a dual inhibitor of cyclo-oxygenase and 5-lipoxygenase, a promising alternative in anti-inflammatory therapy? Fundam Clin Pharmacol 2004; 18: 125-30
30. Day RO, Quinn DI, Conaghan PG, et al. Adverse drug reactions and their measurement in the rheumatic diseases. J Rheumatol 1995; 22: 983-8
31. Lasser KE, Allen PD, Woolhandler SJ, et al. Timing of new black box warnings and withdrawals for prescription medications. JAMA 2002; 287: 2215-20

Correspondence and offprints: Professor *Bernard Bannwarth*, Service de Rhumatologie, Groupe Hospitalier Pellegrin, 33076 Bordeaux Cedex, France.
E-mail: bernard.bannwarth@u-bordeaux2.fr